The substitute Sequence Listing includes the most recent application information that was not made part of the original Sequence Listing. The amendments to the Specification are being made to reference the sequences found in the specification by their SEQ ID NOS. These amendments are editorial in nature and do not constitute new matter.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Attachments: Paper and disk copy and of Sequence Listing
Copy of Notice to Comply
Copy of Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph beginning on page 45, line 19 has been amended as follows:

--To this peptide resin, 2 ml of Reagent K (5% phenol, 5% thioanisole, 5% H_2O, and 2.5% ethanedithiol in TFA) was added and allowed to react for 2.5 hours at room temperature. While cooling with ice, 10 ml of diethyl ether was added to the reaction, the mixture was stirred for 10 minutes, filtered, and then washed with 10 ml of diethyl ether. To the filter cake, 10 ml of 10% acetic acid aqueous solution (hereinafter referred to as aqueous acetic acid) was added and the mixture was stirred for 30 minutes. The resin was then filtered, and washed with 4 ml of aqueous acetic acid. After lyophilizing the filtrate and the wash, the crude peptide obtained was dissolved in aqueous acetic acid, and injected into a reverse phase packing material COSMOSIL 5C18-AR column (25 ϕ x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased up to 25% over 260 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 11.7 mg of Lys-Phe-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO:1).--

The paragraph beginning on page 46, line 11 has been amended as follows:

--The peptide obtained, Lys-Phe-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO:1), had a retention time of 23.9 minutes in an analysis using a reverse phase packing material YMC-PACK ODS-AM column (4.6 ϕ x 250 mm) eluted with a linear gradient of acetonitrile concentration from 0 to 60% containing 0.1% TFA,

and the results of amino acid analysis and mass spectrometry of the product were consistent with the theoretical values.--

The paragraph beginning on page 47, line 22 has been amended as follows:

--Synthesis of Asp-Phe-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO: 2)

In the same manner as that described in Example 5, using 100 mg of Fmoc-Phe-Alko Resin, Fmoc-Asp (OtBu)-OH, Fmoc-Gly-OH, Fmoc-Gly-OH, Fmoc-Gln-OH, Fmoc-Ile-OH, Fmoc-Met-OH, Fmoc-Phe-OH, and Fmoc-Asp(OtBu)-OH were coupled in order, and the product was then deprotected. The crude peptide obtained was dissolved in aqueous acetic acid and injected into a reverse phase packing material COSMOSIL 5C18-AR column (25 ϕ x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased up to 31% over 260 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 3.6 mg of Asp-Phe-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:2).--

The paragraph beginning on page 48, line 10 has been amended as follows:

--The peptide obtained, Asp-Phe-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:2), had a retention time of 25.8 minutes in an analysis using a reverse phase packing material YMC-PACK ODS-AM column (4.6 ϕ x 250 mm) eluted with a linear gradient of acetonitrile concentration from 0 to 60% containing 0.1% TFA,

and the results of amino acid analysis (Met being not detected) and mass spectrometry of the product were consistent with the theoretical values.--

The paragraph beginning on page 50, line 2 has been amended as follows:

--The peptide Lys-Tyr-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO: 39) was synthesized in the same manner as that described in Example 5. Specifically, using 100 mg of Fmoc-Phe Alko Resin, Fmoc-Asp (OtBu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ile-OH, Fmoc-Val-OH, Fmoc-Arg(Pmc)-OH, Fmoc-His(Trt)-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Lys(Boc)-OH were coupled in order, and the product was then deprotected. The crude peptide obtained was dissolved in aqueous acetic acid and injected into a reverse phase packing material COSMOSIL 5C18-AR column (25 ϕ x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased up to 25% over 200 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 44.9 mg of Lys-Try-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO:39).--

The paragraph beginning on page 50, line 17 has been amended as follows:

--The peptide obtained Lys-Tyr-His-Arg-Val-Ile-Lys-Asp-Phe (SEQ ID NO:39) had a retention time of 17.7 minutes in an analysis using a reverse phase packing material YMC-PACK ODS-AM column (4.6 ϕ x 250 mm) eluted with a

linear gradient of acetonitrile concentration from 0 to 60% containing 0.1% TFA, and the results of amino acid analysis and mass spectrometry of the product were consistent with the theoretical values.--

The paragraph beginning on page 51, line 15 has been amended as follows:

--Synthesis of Asp-Tyr-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO: 40)

In the same manner as that described in Example 5, using 100 mg of Fmoc-Phe-Alco Resin, Fmoc-Asp (OtBu)-OH, Fmoc-Gly-OH, Fmoc-Gly-OH, Fmoc-Gln-OH, Fmoc-Ile-OH, Fmoc-Met-OH, Fmoc-Tyr(tBu)-OH, and Fmoc-Asp(OtBu)-OH were coupled in order, and the product was then deprotected. The crude peptide obtained was dissolved in aqueous acetic acid and injected into a reverse phase packing material COSMOSIL 5C18-AR column (25 ϕ x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased up to 27% over 200 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 12.8 mg of Asp-Tyr-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:40).--

The paragraph beginning on page 52, line 3 has been amended as follows:

--The peptide obtained Asp-Tyr-Met-Ile-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:40) had a retention time of 24.7 minutes in an analysis using a reverse phase packing material YMC-PACK ODS-AM column (4.6 ϕ x 250 mm) eluted with a linear gradient of acetonitrile concentration from 0 to 60% containing 0.1% TFA,

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and the results of amino acid analysis (Met being not detected) and mass spectrometry of the product were consistent with the theoretical values.--

The paragraph beginning on page 56, line 7 has been amended as follows:

--To this peptide resin, 1 ml of Reagent K (5% phenol, 5% thioanisole, 5% H_2O, and 2.5% ethanedithiol in TFA) was added and allowed to react for 2.5 hours at room temperature. While cooling with ice, 10 ml of diethyl ether was added to the reaction, the mixture was stirred for 10 minutes, filtered, and then washed with 10 ml of diethyl ether. To the filter cake, 10 ml of aqueous acetic acid was added and the mixture was stirred for 30 minutes. The resin was then filtered, and washed with 4 ml of aqueous acetic acid. After lyophilizing the filtrate and the wash, the crude peptide obtained was dissolved in aqueous acetic acid, and injected into a reverse phase packing material YMC-PACK ODS-A SH-363-5 (30 ϕ x 250 mm) pre-equilibrated with 0.1% aqueous TFA. The column was washed with 0.1% aqueous TFA, and the concentration of acetonitrile was then increased from 0 to 15% over 60 minutes and from 15% to 30% over 240 minutes to elute the product at a flow rate of 7 ml/min. The eluate was monitored by A 220 nm. The fractions containing the desired product were combined together and lyophilized to obtain 9.7 mg of Gly-Phe-Met-Cys-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:41).--

The paragraph beginning on page 56, line 25 has been amended as follows:

--The peptide obtained, Gly-Phe-Met-Cys-Gln-Gly-Gly-Asp-Phe (SEQ ID NO:41), was analyzed using a reverse phase packing material YMC-PACK ODS-

AM AM303 (4.6 ϕ x 250 mm), and proved to have a retention time of 18.8 minutes with a linear gradient of acetonitrile concentration from 18% to 48% containing 0.1% TFA. The results of amino acid analysis (Cys could not be detected) and mass spectrometry of the product were consistent with the theoretical values.--

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